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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,688	01/07/2002	Yong Hua Zhu	LOMAU.143A	5449

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,688	ZHU ET AL.	
	Examiner	Art Unit	
	Isis Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/11/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10-18,20,22-24,26-29 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,10-18,20,22-24,26-29 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O

DETAILED ACTION

The receipt is acknowledged of applicants' amendment, and declaration, both filed 04/11/2005.

Claims 1-6, 8, 10-18, 20, 22-24, 26-29, 31-34 are pending and included in the prosecution.

The following new ground of rejection is necessitated by applicants' amendment:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-6, 8, 10-18, 20, 22-24, 26-29, 31-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment of the claim to recite "stable" has introduced new matter. Recourse to the specification, no disclosure of stable liquid adhesive composition.

The following rejection were discussed in details in the previous office action and maintained for reasons of record:

Claim Rejections - 35 USC § 103

3. Claims 1, 4, 5, 8, 12, 13, 16, 17, 20, 26-29, 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/10374 ('374) in view of US 4,919,939 ('939).

WO '374 discloses *in situ* polymerizing (*in situ* curing) biomedical implant material and a method for repair of mammalian tissue using the same biomedical material (abstract; page 8, line 35; page 9, line 1). The material comprises cyanoacrylate adhesive, hydrophilic porosifying agent and antibiotic (page 6, lines 9, 16-17; page 7, line 1; page 8, line 23 till page 9, line 2). The hydrophilic porosifying agent includes polyethylene glycol that dissolve *in situ* as a result of exposure to an aqueous environment, e.g. body fluids are aqueous (page 4, lines 20-23). The *in situ* polymerizing implant material is introduced into the repair site (reads on wound) by variety of means and is used as a sealant in anatomic regions where it would be difficult to use a pre-cast dressing (page 12, lines 12-19). Introducing the *in situ* polymerizing implant material into the repair site reads on the step of "approximating the wound" in claim 12. Polymerization *in situ* reads on the step of curing the adhesive in claim 12. The adhesive material is a liquid as implied by its application at the site by pouring (page 12, lines 12-15).

The reference does not teach encapsulating the active substance or the material of the capsule. Although the reference teaches that the porosifying agent dissolves in

the aqueous environment, i.e. the body fluid, however, the reference does not teach the delivery of the substance to the tissue.

It is implied from the teaching of the reference that an active agent is delivered, such as anti-microbials including penicillin (page 12, lines 22-30). It is expected from the implanted composition that polymerizes *in situ* and comprises hydrophilic pore forming agent and active substance, to deliver the substance through the pores after the pore-forming agent dissolves.

US '939 teaches a controlled release and self retaining drug delivery device that incorporate drug-containing microcapsules in fluid carrier medium and is effective in the environment of use up to 30 days (abstract; col.1, lines 16-18; col.4, lines 1-3). The microcapsules contain antibiotics such as penicillin and amoxicillin (col.5, lines 44, 52-56). The microcapsules comprise gelatin (col.7, line 7). The microcapsules are incorporated in a matrix of cyanoacrylate (col.11, line 15).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a composition and a method for sealing wound by applying composition comprising cyanoacrylate, pore forming agent and antibiotic where the antibiotic as disclosed by WO '374, and encapsulate the antibiotic in gelatin capsule as disclosed by US '939, motivated by the teaching of US '939 that encapsulated active agent provide prolonged controlled release of the active agent, with reasonable expectation of the delivered wound sealing composition to deliver antibiotic to the wound in a controlled prolonged manner that prevents sepsis of the wound with its subsequent drawbacks.

Response to Arguments

Applicant's arguments filed 04/11/2005 have been fully considered but they are not persuasive. Applicants traverse the above U.S.C.103 (a) rejection above by arguing that WO '374 does not teach stable liquid composition, but solid composition or the microencapsulation of the antibiotics, and both WO '374. WO '374 does not teach the pore-forming agent for delivering the active agent, but for assisting in fluid flux to the matrix. None of WO '374 and US '393 teach particular antibiotics would impact the form of the composition and none of the references recognized that the premature polymerization is an issue when antibiotics are mixed with a cyanoacrylate. No motivation to combine the references. A *prima facie* case of obviousness cannot be made.

In response to the above applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The primary reference teaches each element of the composition, except for the microencapsulation of the active agent, i.e. teaches liquid composition comprising cyanoacrylate, PEG, and antibiotic, and the secondary reference is relied upon for the solely teaching of the microencapsulation of the active agent in a wound dressing to achieve controlled release as desired by applicants. WO '374 teaches liquid composition as implied by its application at the site by pouring and

its solidification in situ. US '393 teaches on col.3, line 26 that the polymer carrier for the microcapsules is fluid. Therefore, the references teach the liquid composition. And combination of the references teaches the invention as a whole. The examiner has noted that the claims are directed into composition and all the elements of the composition are taught by the combined teachings of the references, and the intended use of the individual ingredients does not impart patentability to the claims. The rationale to modify the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art and the reason to modify the reference may often suggest what the applicant has done even for a different reason. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one having ordinary skill in the art would have been motivated by the teaching of US '939 that encapsulated active agent provide prolonged controlled release of the active agent, with reasonable expectation of the delivered wound sealing composition to deliver antibiotic to the wound in a controlled prolonged manner that prevents sepsis of the wound with its subsequent drawbacks. It has been held that a prior art reference must either be in

the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, both references are in the field of applicants' endeavor and concerned to the same problem as applicants, which problem is the controlled release of the active agent as per applicants' disclosure at page 11, line 23. In the examiner opinion, prima facie case of obviousness has been established.

4. Claims 2, 3, 14, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '939 and further in view of US 5,811,091 ('091).

The teachings of WO '374 in view of US '939 are discussed above.

WO '374 in combination with US '939 do not teach the cyanoacrylate as butyl or octyl cyanoacrylate as in claims 2, 3, 14, and 15.

US '091 teaches a composition comprising cyanoacrylates with the most preferred compounds include butyl and octyl cyanoacrylate because they bond the human skin tissue without causing histotoxicity or cytotoxicity (col.5, lines 26-49). The composition is useful for topically covering non-suturable wounds (col.8, line 4).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to deliver the composition for wound sealing comprising cyanoacrylate, pore forming agent and encapsulated active substance as disclosed by WO '374 in view of US '939, and select butyl and octyl cyanoacrylate as taught by US '091, motivated by the teaching of US '091 that the butyl and octyl cyanoacrylate bond

the human skin tissue without causing histotoxicity or cytotoxicity, with reasonable expectation of having a safe compatible wound sealing composition that successfully seals non-suturable wounds.

Response to Arguments

Applicant's arguments filed 04/11/2005 have been fully considered but they are not persuasive. Applicants traverse the above U.S.C.103 (a) rejection above by arguing that US '091 does not overcome the deficiencies of WO '374 in combination with US '393 as it only teaches butyl and octyl cyanoacrylate for sealing wounds and does not include any teachings as to preparation of a stable liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). WO '734 and US '393 in combination teaches the present invention, and US '091 is relied upon for the solely teaching of the species of the cyanoacrylate and to show that they are known in the wound dressing art. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443,

24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all the cited references are in the field of applicants' endeavor and concerned to the same problem as applicants, which problem is wound dressing comprising octyl and butyl cyanoacrylate.

5. Claims 2, 3, 10, 11,14, 15, and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view of US '939 and further in view of WO 96/00760 ('760).

The teachings of WO '374 in view of US '939 are discussed above.

WO '374 in view of US '939 do not teach the cyanoacrylate as butyl or octyl cyanoacrylate as in claims 2, 3, 14, and 15; the anti-degradation agents claimed in claims 10, 11, 23 and 24; or the wound as a lacerated wound as in claim 22.

WO '760 teaches a biocompatible composition comprising pH modifier and cyanoacrylate monomer useful as biomedical and surgical adhesive and sealant (abstract; page 5, line 17). The advantageous monomers of the composition are butyl and octyl cyanoacrylate, as claimed in claims 2, 3, 14, 15, as they form a composition of adequate flexibility and strength to withstand normal movement of the tissue and a bond strength that is maintained as natural tissue healing proceeds (page 6, lines 15-19; page 18, lines 23-32). The pH modifier regulates the polymer biodegradation by regulating the pH of the in vivo environment of the biocompatible composition and makes it proceeds more slowly than it does at a physiological pH, this reads on anti-degradation agents claimed in claims 10 and 23, resulting in retarding the rate of release of the degradation products, thereby reducing their toxic effects (page 3, lines

27-29; page 9, lines 28-35). PH modifiers include ascorbic aid (vitamin C), claimed in claims 11 and 24 (page 10, line 26). The compositions of the reference find uses in traumatically lacerated tissues, claim 22 (page 4, lines 6-12).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using composition comprising cyanoacrylate, pore forming agent and encapsulated active substance as disclosed by WO '374 in view of US '939 and select the octyl and butyl cyanoacrylate monomers as they are preferred by WO '760 because the compositions comprising them are useful as tissue adhesive or sealants that find uses in traumatically lacerated tissues, a function desired by applicants, and they form a composition of adequate flexibility and strength that is maintained as natural tissue healing proceeds, and also one having ordinary skill in the art would have been motivated to add anti-degradation agents such as vitamin C disclosed by WO '760 to the sealing composition of WO '374 in combination with US '939 motivated by the teaching of WO '760 that these compounds regulate the polymer biodegradation and make it proceeds more slowly than it does at a physiological pH resulting in retarding the rate of release of the degradation products, thereby reducing their toxic effects with reasonable expectation of having safe non toxic wound sealant with sustained sealing effect.

Response to Arguments

Applicant's arguments filed 04/11/2005 have been fully considered but they are not persuasive. Applicants traverse the above U.S.C.103 (a) rejection above by arguing

that WO '760 does not include any teachings as to preparation of a stable liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). WO '734 and US '393 in combination teaches the present invention, and WO '760 is relied upon for the teaching of the species of the cyanoacrylate and to show them as known in the wound dressing art, and also for the teaching of anti-degradation agents incorporated in wound dressings to treat lacerated wounds. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all the cited references are in the field of applicants' endeavor and concerned to the same problem as applicants, which problem is wound dressing comprising octyl and butyl cyanoacrylate and anti-degradation agents.

6. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '374 in view US '939 and further in view of WO 99/20685 ('685).

The teachings of WO '374 in view of US '939 are discussed above.

WO '374 in view of US '939 do not teach the molecular weight of the polyethylene glycol as claimed in claims 6 and 18.

WO '685 teaches a formulation that forms a film comprising water soluble pore forming agent such as polyethylene glycol that leaches out through the film *in situ* and creates a perforations that regulate the release rate of active agents (page 7, lines 10-16). The preferable molecular weight of the polyethylene glycol that is able to create adequate pore size for controlling the release of the active agents is from 540 to 8000, i.e. encompasses the molecular weight claimed by applicants in claims 6 and 18 (page 9, lines 23-28; page 10, lines 1-2).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide composition and method for sealing the wound using composition comprising cyanoacrylate, polyethylene glycol as pore forming agent and encapsulated active substance as disclosed by WO '374 in view of US '939 and select the molecular weight of the polyethylene glycol between 540 and 8000 as taught by WO '685 because this range of molecular weight is preferred by the WO '685 because of the ability of polyethylene glycol having such molecular weight to create adequate pore size for controlling the release of the active agents, with reasonable expectation of success of the delivered wound sealing composition to deliver active agents at a controlled rate to the wound site with success.

Response to Arguments

Applicant's arguments filed 04/11/2005 have been fully considered but they are not persuasive. Applicants traverse the above U.S.C.103 (a) rejection above by arguing that WO '685 does not include any teachings as to preparation of a liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). WO '734 and US '393 in combination teaches the present invention, and WO '685 is relied upon for the solely teaching the specific molecular weight of PEG and to show them as known in the wound dressing art as pore forming agents. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all the cited references are in the field of applicants' endeavor and concerned to the same problem as applicants, which problem is wound dressing comprising cyanoacrylate and PEG of specific molecular weight as a pore-forming agent.

Response to Amendment

7. The declaration under 37 CFR 1.132 filed 04/11/2005 is insufficient to overcome the rejection of claims 1-6, 8, 10-18, 20, 22-24, 26-29, and 31-34 based upon being obviousness under 103 (a) rejection as set forth in the last Office action because: it states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04. The result of encapsulation as to block the undesired polymerization of cyanoacrylate is obvious and it is expected to protect cyanoacrylate (Crazy Glue) from contact with the active agents, see US 6,207,193 for Pellegrini. Also US '393 disclosed encapsulated antibiotic in polymer carrier including cyanoacrylate. Therefore, the art recognized encapsulation of active agents in a polymer matrix. In addition, the controlled prolonged release that had been achieved by the prior art as a result of encapsulation, US '393, is also desired by applicants as per their disclosure, page 11, line 23-24. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis Ghali
Examiner
Art Unit 1615

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THURMAN K. PAGE
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